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Post-transplant inotrope score is associated with clinical outcomes after adult heart transplantation

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Abstract

Background: Inotrope score has been proposed as a marker of clinical outcome after adult heart transplantation (HTx) but is rarely used in practice.

Methods: Inotrope score during the first 48 h after HTx was calculated in 81 patients as: dopamine + dobutamine + amrinone + milrinone (dose × 15) + epinephrine (dose × 100) + norepinephrine (dose × 100) + enoximone + isoprenaline (dose × 100), with each drug in μg/kg/min. Determinants of inotrope score were identified with linear regression. Cox regression was used to determine the association of inotrope score with mortality.

Results: The mean recipient age was 52 ± 11 years, and 32 (39.5%) patients were female. Determinants of inotrope score were preoperative C-reactive protein, serum urea, congenital heart disease, and donor cardiac arrest (R^2 = .30). Inotrope score was associated with 5-year mortality, independent of recipient age and gender (HR 1.03, 95% CI 1.00-1.07). This association was attenuated when adjusting for female-to-male transplant and ischemia time. Inotrope score was also strongly associated with continuous veno-venous hemofiltration (OR 1.07, 95% CI 1.03-1.12).

Conclusion: High inotrope score post-HTx was observed in recipient congenital heart disease and was associated with a higher risk of mortality and acute kidney injury.

KEYWORDS
assist device, continuous veno-venous hemofiltration, heart transplantation, inotropic agents, ischemia time, mechanical circulatory support, primary graft dysfunction, urea, vasopressors

1 | INTRODUCTION

Heart transplantation (HTx) is the final therapeutic option in end-stage heart failure.[1] Over the last decades, survival has increased due to advances in donor selection, organ preservation and prevention, and management of rejection.[2] Nonetheless, early mortality in the first year after transplantation remains high, mainly due to primary graft dysfunction.[3,4] In a consensus statement concerning primary graft dysfunction, the International Society of Heart and Lung Transplantation (ISHLT) introduced the use of an inotrope score to classify mild to moderate left ventricular primary graft dysfunction.[3] Inotrope score has first been described by Wernovsky as a method of quantifying circulatory support in the postoperative phase after arterial switch operation in neonates.[5] The score combines several

inotropes and vasopressors with different weight factors in one formula, resulting in an objective value allowing comparison of patients receiving different combinations and dosages of inotropes and vasopressors. Several studies have used inotrope score in different modified versions since its initial description, and have shown that it has prognostic value.[6-10] In pediatric heart recipients, high inotrope scores have been associated with adverse short-term outcomes, including prolonged length of hospital stay and renal failure.[8] In adult heart recipients, high inotrope scores are more common in patients with primary graft dysfunction, suggesting inotrope score is a marker of disease severity.[11] However, data concerning the association of post-transplant inotrope score with clinical outcomes in adult heart recipients are scarce. Moreover, there are no data regarding the association of inotrope score with long-term outcomes. The aim of this study was to identify determinants of inotrope score after adult HTx, and whether inotrope score is associated with outcomes after HTx, particularly mortality, the requirement of renal replacement therapy, and cardiac function after HTx.

2 | METHODS

2.1 | Study population

This retrospective study was conducted at the University Medical Center Groningen. All patients gave informed consent for the heart transplant procedure and the use of their data for associated research. Given the retrospective nature of this study, no formal institutional review board approval was required according to the Dutch Medical Research with Human Subjects Law. Between January 2007 and June 2020, a total number of 88 adult heart transplants were performed in our center. Five patients were excluded because administered amounts of inotropes were insufficiently or ambiguously reported in the post-transplant intensive care unit charts. In addition, two patients deceased during the transplant procedure and were therefore excluded from analysis. In total, 81 patients were included for the analysis.

2.2 | Data collection

2.2.1 | Pre-transplant data

Pre-transplant recipient data were collected from electronic patient records. These data included demographic and anthropometric data, heart failure diagnosis, medical history, medication use prior to transplantation, last laboratory values, and most recent right heart catheterization measurements before transplantation. Last estimated glomerular filtration rate before the transplant was calculated using the CKD-EPI formula. History of device implantation (pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy), left ventricular assist device implantation and inotrope dependency prior to transplantation were also recorded.

2.2.2 | Donor data and intraoperative data

Donor data were retrieved from the Eurotransplant donor database. Donor demographics, medical history, intoxications, cause of death, and presence of cardiac arrest were collected.

Intraoperative data included ischemia time, cardiopulmonary bypass time, and requirement of blood transfusion during transplantation. Ischemia time was defined as the time interval between placement of aortic cross-clamp in the donor and the removal of aortic cross-clamp in the recipient. In addition, we recorded whether donor hearts received oxygenated 15 degrees Celsius Buckberg blood cardioplegia during implantation in addition to flush perfusion preservation with University of Wisconsin solution and storage on ice during transport. In our center, Buckberg blood cardioplegia is administered at regular intervals during implantation to reduce myocardial ischemic damage, in particular when an ischemia time of more than four hours is expected.[12]

2.2.3 | Post-transplant data and outcomes

Post-transplant data included the requirement of continuous venovenous hemofiltration (CVVH), extracorporeal life support (ECLS), maximum in-hospital serum troponin T level, maximum in-hospital serum creatinine level, length of intensive care stay, length of hospital stay, and mortality up to 5 years post-HTx. In addition, hemodynamic values measured every 4 to 6 h were collected from the intensive care unit charts in the first 48-h period after HTx. Hemodynamic variables included pulmonary artery catheter-derived cardiac index, pulmonary artery pressures, invasive arterial blood pressure, heart rate, and central venous pressure. For every patient, the median value during the first 48 h was determined. Complete hemodynamic data were collected in 63 of 81 patients (78%). Data were lacking in the remainder of patients due to inaccurate measurements or ambiguous reporting in paper of intensive care charts. Finally, right heart catheterization measurements performed one year after HTx were collected.

2.2.4 | Calculation of inotrope scores

The amount and dosages of inotropic medication were extracted from post-transplant intensive care charts of the first 48 h after transplantation. In our center, all post-HTx patients receive afterload reduction and right ventricular support using nitric oxide ventilation, as well as inotropes and vasopressors where needed based on clinical assessment of the patient. First, the total amount of each inotropic drug administered in micrograms during the first 48 h after HTx was calculated. Subsequently, the total amount was divided by the patient's body weight at transplantation to determine the amount of each inotropic drug in μg/kg. This was then divided by 2880 min (48 h) to convert the drug dosages to μg/kg/min reflecting the average dosage administered per minute during the first 48 h after HTx. Similarly, dosages were separately calculated for the first

24 h and second 24 h after HTx. In addition, inotrope score at arrival on the intensive care unit post-HTx was calculated for 60 of 81 patients based on the initial infusion rates of all inotropes. Of the remainder of patients (n = 21), only cumulative doses of the first and second 24 h were available. Inotrope scores were calculated using the following formula (Box 1)[11]:

2.3 | Statistical analysis

Data were reported as mean ± standard deviation for continuous parametric data, median [interquartile range (IQR)] for continuous nonparametric data, and number (percentage) for categorical data. Descriptive statistics were performed for all baseline recipient, donor, and intraoperative variables. To compare baseline characteristics and outcomes of patients with different inotrope scores, we divided our cohort in tertiles based on average inotrope score during the first 48 h after HTx. Because inotrope requirements in the immediate period following HTx are relatively high both in patients with and without primary graft dysfunction, inotrope score during the first 48 h was used as persistently high inotrope requirements might better reflect illness severity.[6,8,11,13] Baseline characteristics and post-transplant variables were compared between tertiles with Kruskal–Wallis tests for continuous data and chi-square tests for categorical data.

To identify which variables are determinants of inotrope score, a series of univariate logistic regression models were performed using baseline and intraoperative variables. Variables associated at p ≤ 15 significance level as well as age and gender as possible confounders were included in a multivariable logistic regression model. The final model was selected using manual backward selection at p < .05 significance level.

Log-rank test was used to compare survival between inotrope tertiles. To determine whether inotrope score is an independent predictor of mortality after transplantation, inotrope score was entered as a continuous predictor in a Cox proportional hazards model adjusted for age and gender. In a second model, female-to-male transplant and ischemia time were also included, as these are risk factors associated with primary graft dysfunction. Also, inotrope score was entered as a categorical variable split into tertiles. As inotropic requirements after HTx are influenced by extracorporeal life support, the interaction between inotrope score and ECLS was checked. Cox proportional hazard assumption was checked using Schoenfeld residuals and showed no violation.

> **BOX 1 Calculation of inotrope score**
>
> Inotrope Score = dopamine (dose × 1) + dobutamine (dose × 1) + amrinone (dose × 1) + milrinone (dose × 15) + epinephrine (dose × 100) + norepinephrine (dose × 100) + enoximone (dose × 1) + isoprenaline (dose × 100).

Logistic regression was used to assess the relation between inotrope score and requirement of renal replacement therapy, adjusted for age, gender, female-to-male transplant, and ischemia time. Similarly, linear regression was used to evaluate the association of inotrope score with right heart catheterization variables one year after HTx. Statistical analyses were performed in R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). All p-values were reported two-sided.

3 | RESULTS

In the total cohort, the mean age at HTx was 52 ± 11 years and 32 (39.5%) patients were female. The indication for HTx was ischemic heart failure in 19 (23.5%) patients, congenital heart disease in 5 (6.2%) patients and non-ischemic cardiomyopathy in 57 (70.4%) patients. Prior to transplantation, 22 (27.2%) patients received a left ventricular assist device and 19 (23.5%) patients were dependent on inotropic support before transplantation. Median ischemia time was 223 min [192-241], ranging from 80 to 336 min.

3.1 | Inotropic drugs and inotrope scores

During the first 48 h after HTx, nearly all patients (98%) received norepinephrine and milrinone (Table 1). In addition, 16% of patients received dopamine, 35% received dobutamine, 56% received epinephrine and 11% received isoprenaline.

The median inotrope score was 23.2 [13.7-31.7] during the first 24 h after HTx and 14.5 [7.4-28.2] in the second 24 h (Table 1). The median inotrope score was 19.4 [10.8-28.2] during the first 48 h after HTx. The cohort was divided into tertiles based on average inotrope score during the first 48 h after HTx: first tertile ranged from 2.1 to 12.4, second tertile from 12.5 to 24.4 and third tertile from 24.5 to 75.6.

The distribution of inotrope scores during the first 48 h after HTx is depicted in Figure 1. One patient had a relatively high inotrope score of 75.6. This was a 61-year-old female with a history of autoimmune disease and was listed for heart transplantation because of hereditary endomyocardial fibrosis. After transplantation, this patient developed a systemic inflammatory response with refractive vasoplegia requiring high doses of vasopressors.

3.2 | Baseline recipient, donor, and intraoperative characteristics

Baseline demographics, medical history, and medication use were similar between tertiles (Table 2). Between inotrope score tertiles, there was no difference in the number of patients requiring mechanical circulatory support or continuous inotropic support prior to HTx. High-sensitive C-reactive protein (hsCRP) levels were higher in the third tertile compared to the first tertile (8.0 [4.6, 12.0] versus 5.0

TABLE 1 Inotrope scores and use of inotropes in the first 48 h after heart transplantation

	First Tertile (N = 27)	Second Tertile (N = 27)	Third Tertile (N = 27)	Total (N = 81)
Average Inotrope Scores				
First 24 h	11.8 (8.3, 14.4)	23.2 (19.3, 27.9)	38.1 (31.7, 41.8)	23.2 (13.7, 31.7)
Second 24 h	5.3 (4.1, 7.9)	14.5 (10.7, 18.6)	34.9 (28.6, 39.0)	14.5 (7.4, 28.2)
First 48 h	8.5 (7.1, 10.8)	19.4 (16.0, 23.1)	37.0 (28.5, 41.8)	19.4 (10.8, 28.2)
Number of Patients Receiving				
Dopamine	0 (0.0%)	7 (25.9%)	6 (22.2%)	13 (16.0%)
Dobutamine	9 (33.3%)	12 (44.4%)	7 (25.9%)	28 (34.6%)
Milrinone	25 (92.6%)	27 (100.0%)	27 (100.0%)	79 (97.5%)
Epinephrine	16 (59.3%)	11 (40.7%)	18 (66.7%)	45 (55.6%)
Norepinephrine	25 (92.6%)	27 (100.0%)	27 (100.0%)	79 (97.5%)
Isoprenaline	3 (11.1%)	2 (7.4%)	4 (14.8%)	9 (11.1%)
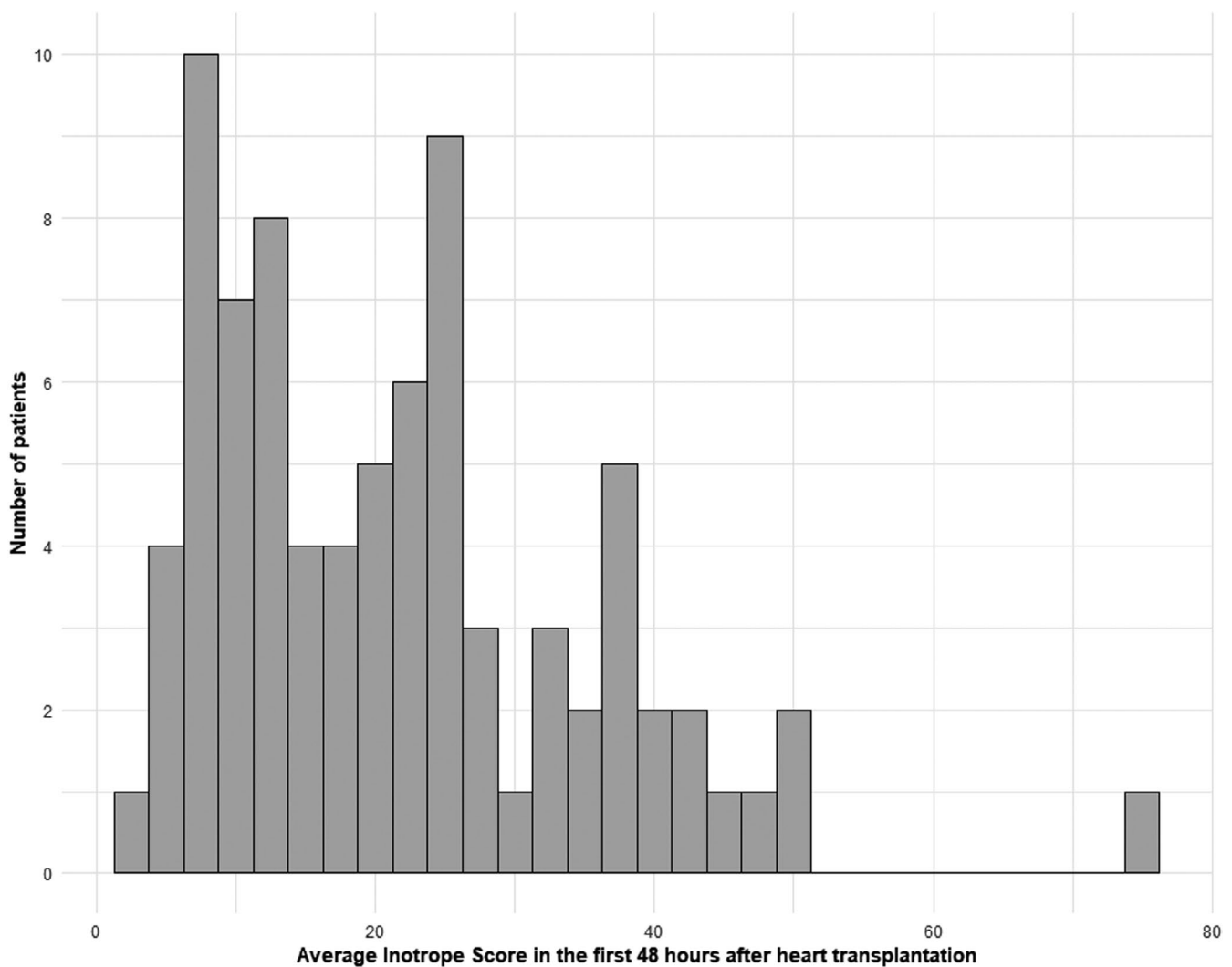
FIGURE 1 Distribution of average inotrope scores during the first 48 h after heart transplantation

[1.4, 6.5], p = .03). Urea levels were also higher in the third tertile compared to the first tertile (10.7 [8.7, 13.9] versus 8.7 [6.2, 10.1], p < .01) and second tertile (10.7 [8.7, 13.9] versus 8.9 [6.3, 10.9], p = .03). Right heart catheterization hemodynamic measurements were similar between tertiles. Baseline donor characteristics and intraoperative characteristics did not differ between tertiles (Table 3).

TABLE 2 Baseline recipient characteristics per inotrope score tertile

	First Tertile (N = 27)	Second Tertile (N = 27)	Third Tertile (N = 27)	p-Value
Age (years)	51.0 (39.5, 60.5)	52.0 (47.5, 62.0)	58.0 (51.0, 61.0)	.24
Female gender	10 (37.0%)	10 (37.0%)	12 (44.4%)	.81
BMI (kg/m^2)	24.8 (22.8, 26.9)	25.7 (22.3, 28.3)	25.0 (22.5, 26.9)	.74
Heart failure diagnosis				.41
Congenital Heart Disease	0 (0.0%)	2 (7.4%)	3 (11.1%)	
Ischemic Cardiomyopathy	5 (18.5%)	7 (25.9%)	7 (25.9%)	
Non-ischemic Cardiomyopathy	22 (81.5%)	18 (66.7%)	17 (63.0%)	
Medical history				
Coronary artery disease	8 (29.6%)	7 (25.9%)	7 (25.9%)	.94
Hypertension	0 (0.0%)	5 (18.5%)	4 (14.8%)	.07
COPD	2 (7.4%)	1 (3.7%)	1 (3.7%)	.77
Diabetes mellitus	1 (3.7%)	1 (3.7%)	3 (11.1%)	.43
Medication				
Beta-blocker	24 (88.9%)	22 (81.5%)	20 (74.1%)	.37
ACE inhibitor or ARB	22 (81.5%)	24 (88.9%)	21 (77.8%)	.55
MRA	17 (63.0%)	16 (59.3%)	13 (48.1%)	.52
Loop diuretic	24 (88.9%)	24 (88.9%)	25 (92.6%)	.87
Vitamin K antagonist	25 (92.6%)	22 (81.5%)	22 (81.5%)	.41
Thrombocyte aggregation inhibitors	6 (22.2%)	9 (33.3%)	10 (37.0%)	.47
Devices and circulatory support				
ICD	18 (66.7%)	22 (81.5%)	19 (70.4%)	.44
CRT	7 (25.9%)	10 (37.0%)	9 (33.3%)	.67
Ventricular assist device	6 (22.2%)	8 (29.6%)	8 (29.6%)	.78
ECLS	1 (3.7%)	1 (3.7%)	2 (7.4%)	.77
Inotrope dependent	4 (14.8%)	5 (18.5%)	10 (37.0%)	.12
Laboratory values				
Hemoglobin (g/dl)	13.5 (12.7, 14.5)	13.9 (11.9, 14.3)	12.3 (10.6, 14.0)	.20
Leucocyte count (10^9/L)	8.1 (7.5, 9.6)	7.4 (5.8, 8.6)	8.2 (7.2, 9.5)	.14
NT-proBNP (pg/ml)	2183 (1071, 4664)	2960 (1202, 4744)	4335 (1924, 6503)	.08
C-reactive protein (mg/L)	5.0 (1.4, 6.5)	5.0 (3.0, 8.8)	8.0 (4.6, 12.0)	.03
Lactate dehydrogenase (U/L)	237.0 (210.0, 304.5)	256.0 (219.5, 293.5)	256.0 (230.0, 326.8)	.54
Creatinine (mg/dl)	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	1.3 (1.1, 1.6)	.12
eGFR (ml/min/1.73 m^2)	55.0 (44.9, 69.0)	49.6 (40.7, 62.4)	45.5 (35.6, 58.1)	.11
Urea (mmol/L)	8.7 (6.2, 10.1)	8.9 (6.3, 10.9)	10.7 (8.7, 13.9)	.02
ALAT (U/L)	26.0 (20.0, 31.5)	24.0 (20.5, 36.5)	23.5 (18.2, 29.2)	.60
ASAT (U/L)	30.0 (23.5, 34.5)	31.0 (26.0, 40.0)	34.0 (24.2, 42.2)	.62
Total bilirubin (μmol/L)	10.0 (7.0, 16.5)	9.5 (8.0, 15.8)	13.5 (9.0, 21.5)	.17
Albumin (g/L)	44.0 (42.0, 46.0)	43.0 (40.5, 46.0)	43.0 (38.0, 44.0)	.21
Pre-transplant hemodynamics				
mRAP (mmHg)	6.0 (3.2, 12.5)	10.0 (7.0, 12.5)	11.0 (7.2, 18.0)	.09
mPAP (mmHg)	19.0 (15.0, 34.5)	25.5 (17.2, 32.8)	25.0 (21.0, 33.0)	.36
mPCWP (mmHg)	14.0 (8.5, 23.0)	16.0 (10.0, 22.5)	18.0 (13.0, 24.5)	.50
PVR (dynes s/cm^5)	117.4 (75.4, 159.9)	134.3 (104.2, 160.7)	149.0 (96.0, 255.1)	.20
Cardiac index (L/min/m^2)	2.2 (1.9, 2.8)	2.5 (2.1, 3.1)	2.1 (1.9, 2.6)	.08

(continues)

TABLE 2 (continued)

	First Tertile (N = 27)	Second Tertile (N = 27)	Third Tertile (N = 27)	p-Value
SBP (mmHg)	95.0 (88.5, 106.5)	95.0 (90.0, 104.0)	100.0 (91.2, 105.8)	.61
DBP (mmHg)	69.0 (61.0, 71.5)	70.0 (60.0, 75.0)	69.0 (60.0, 75.8)	.97

Abbreviations: ACE, angiotensin converting enzyme; ALAT, alanine aminotransferase; ARB, angiotensin receptor blocker; ASAT, asparagine aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; ECLS, extracorporeal life support; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; MRA, mineralocorticoid receptor antagonist; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; SBP, systolic blood pressure.

TABLE 3 Baseline donor and intraoperative characteristics

	First Tertile (N = 27)	Second Tertile (N = 27)	Third Tertile (N = 27)	p-Value
Donor characteristics				
Age (years)	47.0 (28.0, 54.5)	50.0 (45.0, 55.0)	49.0 (38.2, 54.0)	.69
Female gender	9 (39.1%)	12 (44.4%)	14 (58.3%)	.39
Female donor to male recipient	3 (12.5%)	3 (11.1%)	6 (24.0%)	.39
Body mass index (kg/m^2)	23.3 (21.1, 24.9)	24.3 (22.6, 27.3)	24.4 (20.6, 27.2)	.27
Cause of death				.09
Cerebrovascular	11 (47.8%)	16 (59.3%)	12 (50.0%)	
Cardiovascular	0 (0.0%)	0 (0.0%)	1 (4.2%)	
Trauma	10 (43.5%)	6 (22.2%)	4 (16.7%)	
Anoxia	2 (8.7%)	4 (14.8%)	2 (8.3%)	
Other	0 (0.0%)	1 (3.7%)	5 (20.8%)	
Cardiac arrest	4 (17.4%)	9 (33.3%)	10 (41.7%)	.19
Intraoperative characteristics				
Ischemia time (min)	200 (183, 236)	230 (209, 250)	222 (194, 239)	.06
CPB time (min)	207 (171, 226)	196 (179, 244)	246 (200, 278)	.06
Buckberg cardioplegia	19 (70.4%)	18 (66.7%)	17 (63.0%)	.85
Blood transfusion	13 (50.0%)	10 (37.0%)	13 (50.0%)	.55

Abbreviation: CPB, cardiopulmonary bypass.

TABLE 4 Determinants of inotrope score

	Coefficient	Standardized coefficient (beta)	p-Value
Serum urea (mmol/L)	0.89	0.37	<.001
High-sensitive C-reactive protein (ng/L)	0.13	0.27	.011
Congenital heart disease (yes versus no)	17.4	0.33	.002
Donor cardiac arrest (yes versus no)	7.01	0.24	.019

3.2.1 | Determinants of inotrope score

In univariate analysis, preoperative hsCRP, mean right atrial pressure, serum urea, and recipient congenital heart disease were significantly associated with inotrope score. In multivariable analysis, after backward selection including all univariate associated variables (p < .15), recipient serum urea, recipient hsCRP, recipient congenital

heart disease, and donor cardiac arrest were independently associated with inotrope score (R^2 = .30) (Table 4).

3.3 | Association of inotrope score with outcomes after heart transplantation

Between tertiles, cardiac index, pulmonary artery pressures, and central venous pressures were similar (Table 5). However, arterial blood pressures were significantly lower in the second and third tertile. The median value of mean arterial pressure during the first 48 h showed a significant correlation with inotrope score (r = -.59) [Figure S1].

Patients in the first tertile were less likely to require nitric oxide ventilation for more than 48 h after transplantation than patients in the second and third inotrope score tertile (11% versus 44%, p = .01). Compared with the first tertile, maximum in-hospital serum creatinine levels were elevated in patients in the second tertile (1.9 [1.4-2.6] versus 2.6 [2.0-4.4], p < .01) and third tertile (1.9 [1.4-2.6] versus 3.7 [2.4-4.7], p < .01).

TABLE 5 Outcomes after heart transplantation per inotrope score tertile

	First Tertile (N = 27)	Second Tertile (N = 27)	Third Tertile (N = 27)	p-Value
Post-transplant hemodynamics[a]				
Cardiac index (L/min/m^2)	3.0 (2.5, 3.4)	2.9 (2.4, 3.1)	3.0 (2.6, 3.4)	.93
Systolic arterial pressure (mmHg)	105 (98, 118)	99 (94, 104)	95 (86, 100)	<.01
Diastolic arterial pressure (mmHg)	59 (54, 60)	53 (50, 56)	53 (47, 55)	<.01
Mean arterial pressure (mmHg)	73 (68, 81)	67 (66, 70)	65 (62, 68)	<.01
sPAP (mmHg)	30 (25, 32)	31 (26, 40)	34 (30, 40)	.09
dPAP (mmHg)	16 (14, 18)	17 (14, 20)	17 (14, 20)	.72
Central venous pressure (mmHg)	12 (11, 14)	11 (8, 14)	13 (9, 16)	.22
Heart rate (bpm)	90 (90, 97)	90 (86, 100)	90 (90, 99)	.69
In-hospital outcomes				
Inotropes >14 days	1 (3.7%)	1 (3.7%)	4 (14.8%)	.20
NO ventilation >48 h	3 (11.1%)	12 (44.4%)	12 (44.4%)	.01
Peak troponin T (ng/L)[a]	1546 (1286, 2341)	1707 (1395, 3156)	1810 (1369, 3388)	.37
Peak serum creatinine (mg/dl)[a]	1.9 (1.4, 2.6)	2.6 (2.0, 4.4)	3.7 (2.4, 4.7)	<.01
CVVH	3 (11.1%)	11 (40.7%)	21 (77.8%)	<.01
Extracorporeal life support	3 (11.1%)	1 (3.7%)	8 (29.6%)	.02
Length of ICU stay (days)	4.0 (2.2, 6.8)	8.5 (6.0, 13.0)	14.0 (8.5, 23.8)	<.01
Length of hospital stay (days)	21.5 (18.0, 31.8)	31.0 (23.5, 55.5)	51.0 (36.0, 65.5)	<.01
Mortality				
30-day mortality	1 (3.7%)	1 (3.7%)	3 (11.1%)	0.43
1-year mortality	2 (7.4%)	4 (14.8%)	7 (25.9%)	0.18
5-year mortality	3 (11.1%)	5 (18.5%)	8 (29.6%)	0.23
Right heart catheterization measurements (1 year post-HTx)				
Cardiac index (L/min/m^2)	3.8 (3.1, 4.0)	3.2 (3.0, 3.6)	3.5 (2.9, 3.8)	.43
sPAP (mmHg)	22.5 (20.0, 24.2)	26.0 (21.0, 30.0)	30.0 (22.0, 34.0)	.10
mRAP (mmHg)	3.0 (0.8, 6.0)	5.0 (3.0, 7.0)	5.0 (1.5, 7.5)	.16
PVR (dynes s/cm^5)	90.3 (71.2, 103.0)	93.7 (83.0, 109.5)	96.3 (70.0, 117.6)	.83

Abbreviations: CVVH, continuous venovenous hemofiltration; dPAP, diastolic pulmonary artery pressure; ICU, intensive care unit; mRAP, mean right atrial pressure; NO, nitric oxide; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure.
[a]Median value during the first 48 h postoperatively. Data from 63 of 81 (78%) patients.

The proportion of patients requiring ECLS was higher in the third tertile than in the second and first tertile (29.6% versus 3.7% and 11.1%, respectively). Upon arrival on the intensive care unit, patients with and without ECLS had similar inotrope scores (35.2 [22.9-47.2] versus 27.3 [15.0-41.9], p = .48). However, the median inotrope score was higher in patients requiring ECLS than in patients without mechanical circulatory support in the first 24 h (36.7 [18.2-40.7] versus 21.9 [13.3-29.7], p = .03) as well as in the second 24 h (36.5 [9.0-40.4] versus 13.9 [7.4-22.8], p = .04) (Figure S2).

Patients in the first tertile had a lower risk of requiring CVVH than patients in the second tertile (11% versus 41%, p = .04) in the third tertile (11% versus 78%, p < .01). Additionally, the median length of intensive care stay was significantly shorter in patients in the first tertile compared with patients in the second tertile (4.0 versus 8.5 days, p < .01) and third tertile (4.0 versus 14.0 days, p < .01). The proportion of patients requiring ECLS was significantly lower in the second tertile compared to the third tertile (4% versus 30%,

p = .02). Mortality in the first 30 days, 1 year, and 5 years after HTx did not differ between tertiles. Also, right cardiac catheterization measurements 1-year post-HTx were similar between tertiles.

3.3.1 | Association of inotrope score with mortality

In univariate analysis, inotrope score in the first 48 h was a significant predictor of 5-year mortality (hazard ratio [HR] per unit increase 1.04, 95% confidence interval [CI] 1.01-1.07) (Table 6). In a multivariable model adjusted for age and gender, inotrope score remained a significant predictor of 5-year mortality (HR 1.03 per unit increase, 95% CI 1.00-1.07). However, in a multivariable model adjusted for age, gender, female-to-male transplant, and ischemia time, this association was attenuated (HR 1.03, 95% CI 1.00-1.06).

Inotrope score entered as a categorical variable based on tertiles was not a significant predictor of 5-year mortality (Figure 2). There

was significant positive interaction between inotrope score tertiles and ECLS after transplantation. Patients without ECLS in the second and third inotrope score tertile had a lower risk of mortality than patients in the second and third tertile who did require ECLS.

3.3.2 | Association of inotrope score with continuous veno-venous hemofiltration and 1-year right heart catheterization measurements

In most patients (78%), CVVH was initiated more than 48 h after HTx. Average inotrope score during the first 48 h after HTx was a significant predictor of CVVH more than 48 h after HTx adjusted for age, gender, female-to-male transplant, and ischemia time (odds ratio 1.07 [1.02-1.12]). Inotrope score was not associated with 1-year cardiac index, pulmonary vascular resistance, or right atrial pressure.

4 | DISCUSSION

We aimed to evaluate the determinants of average inotrope score during the first 48 h after HTx and the association of inotrope score

TABLE 6 Association of inotrope scores with 5-year mortality after transplantation

	Hazard Ratio (95% CI)	p-Value
Univariable		
Inotrope Score 48 h[a]	1.04 (1.01-1.07)	.02
Tertiles Inotrope Score (24 h)		
First Tertile	1.00 (Ref)	
Second Tertile	1.73 (0.42-7.25)	.45
Third Tertile	3.03 (0.80-11.41)	.10
Multivariable model 1[b]		
Inotrope Score 48 h[a]	1.03 (1.00-1.07)	.03
Tertiles Inotrope Score		
First Tertile	1.00 (Ref)	
Second Tertile	1.62 (0.38-6.81)	.51
Third Tertile	2.53 (0.66-9.63)	.17
Multivariable model 2[c]		
Inotrope Score 48 h[a]	1.03 (1.00-1.06)	.09
Tertiles Inotrope Score		
First Tertile	1.00 (Ref)	
Second Tertile	1.55 (0.65-6.70)	.56
Third Tertile	2.12 (0.47-8.40)	.29

Abbreviations: CI, confidence interval; Ref, reference category.
[a]Inotrope score entered in Cox proportional hazards model as continuous variable.
[b]Multivariable model 1 was adjusted for age and gender.
[c]Multivariable model 2 was adjusted for age, gender, female-to-male transplant and ischemia time.

with clinical outcomes after HTx. Our findings show that congenital heart disease, serum urea level, C-reactive protein level, and donor cardiac arrest were independent determinants of inotrope score. Inotrope score was associated with clinical outcomes, including 5-year mortality, continuous veno-venous hemofiltration, and length of intensive care stay.

4.1 | Development of inotrope score

Different versions and modifications of the calculation of inotrope score have been used previously. Inotrope score has first been described in 1995 by Wernovsky et al as a method to compare total inotrope dose in neonates and infants after arterial switch operation with circulatory arrest or with low-flow cardiopulmonary bypass.[5] A modified inotrope score calculation was then introduced in a study that evaluated the usefulness of the inotrope score as a marker for survival after cardiac arrest in infants after cardiac surgery.[14] This study showed that inotrope score was associated with mortality after cardiac arrest. Subsequent clinical studies in pediatric cardiac surgery then used inotrope score in different modifications as a marker of illness severity.[15-18] Gaies et al introduced an updated version of the inotrope score (vasoactive inotrope score [VIS]), which included additional vasoactive drugs commonly used in clinical practice, and showed that maximum VIS in 48 h after pediatric cardiac surgery was strongly associated with poor outcome (mortality, cardiac arrest, mechanical circulatory support, renal replacement therapy and/or neurologic injury).[6] The ability of VIS to predict short-term clinical outcomes was confirmed prospectively in infants undergoing pediatric cardiac surgery.[7] In pediatric HTx patients, high VIS scores at 48 h after HTx were associated with longer intensive care stay, longer intubation time, and higher incidence of renal failure than low VIS scores.[8]

Most clinical studies that applied inotrope score have been performed in the pediatric population. In adult patients, VIS has also proven to be an accurate predictive marker of outcome after cardiac surgery and may perform better in predicting outcome than intensive care scoring systems commonly used in clinical practice.[10,19] Similarly, in left ventricular assist device (LVAD) recipients, the inotrope score was a better predictor of mortality than existing LVAD risk models.[20]

4.2 | Inotrope score in heart transplantation

The International Society of Heart and Lung Transplantation implemented inotrope score in its consensus definition of primary graft dysfunction after HTx.[3] In a prospective study by Dronavalli et al that validated a clinical definition of primary graft dysfunction conceptually similar to the ISHLT definition, inotrope score was significantly higher in patients with primary graft dysfunction.[11] We used the same calculation for inotrope score used by Dronavalli et al, as this study was also conducted in adult heart transplant recipients and
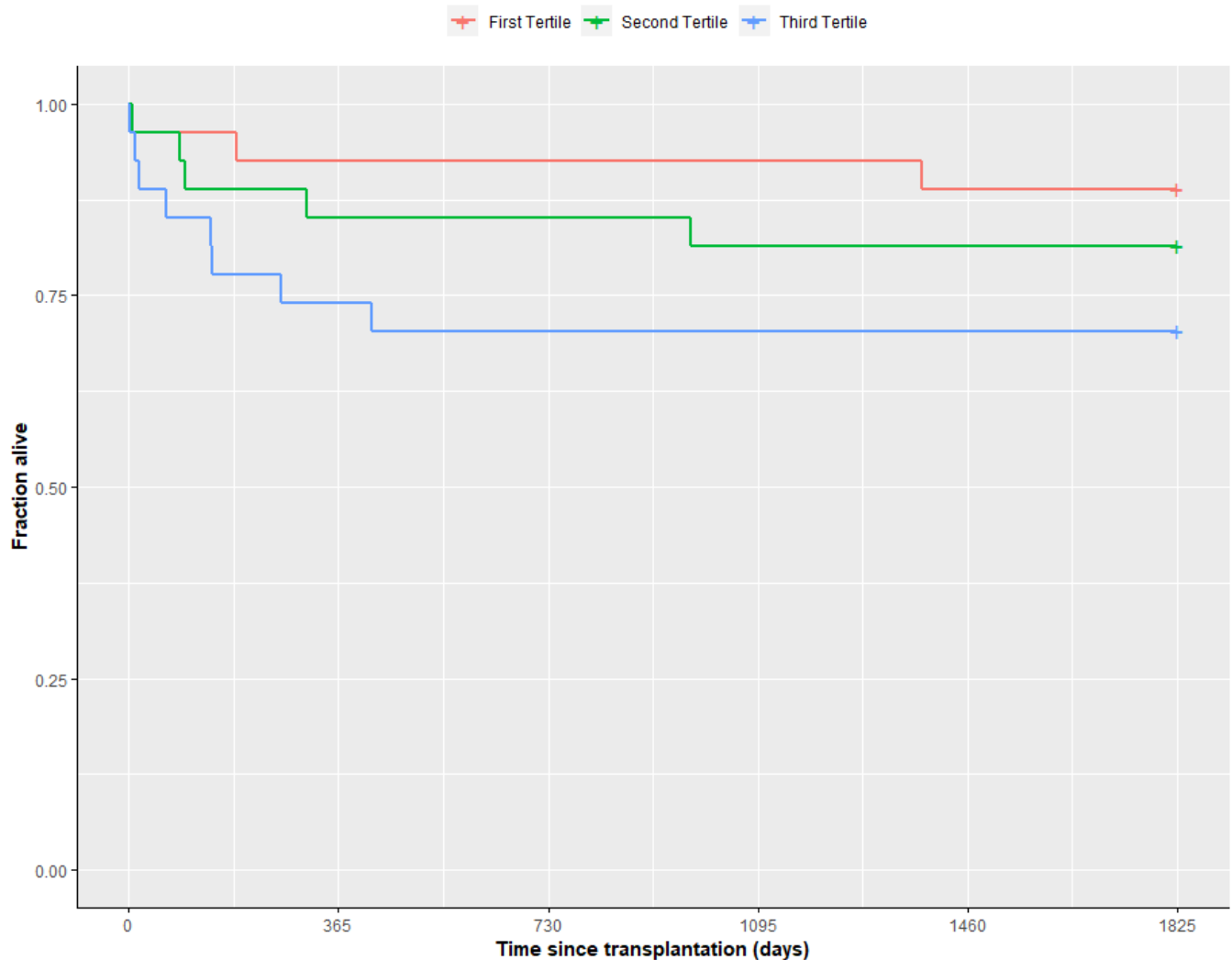
FIGURE 2 Five-year survival after heart transplantation stratified by inotrope score tertile

showed that a high inotrope score is associated with primary graft dysfunction and therefore with clinical outcomes. Many risk factors have been implicated for primary graft dysfunction.[3,21] In line with this, the main determinants of inotrope score that we identified are known risk factors of primary graft dysfunction. Although prolonged ischemia time is a known risk factor for primary graft function, ischemia time was not correlated with inotrope score in our study.[22] It should be noted that median ischemia time was 223 min and ischemia times were homogeneously distributed in our sample, with ischemia time over three hours present in 83% of cases. This is similar to the median ischemia time of 3.2 h in the ISHLT Transplant Registry.[2] Nonetheless, inotrope scores in our study were relatively high with a median of 23.2 at 24 h and 19.4 at 48 h. The ISHLT primary graft dysfunction consensus defines high inotrope requirements as an inotrope score > 10.[3] In the study by Dronavalli et al, median inotrope score was notably lower at 24 h with 10.7 in patients classified with primary graft dysfunction and 5.9 in patients without primary graft dysfunction.[11] Moreover, median inotrope score was 7.6 in patients with primary graft dysfunction and 2.5 in

patients without primary graft dysfunction at 48 h. Median donor age in the aforementioned study was 38 years, 64% of donors were male and 14% of donors had previous cardiopulmonary resuscitation. In addition, recipient age was 43 years at transplant. In our donor population, median age was 50 years, 53% of donors were male and 33% of donors required cardiopulmonary resuscitation. Also, median recipient age was 53 years in our sample. These differences in donor and recipient characteristics might explain the discrepancy in median inotrope scores at 24 and 48 h with our study, although donor age, donor gender, and recipient age were no significant determinants of inotrope score. However, donor cardiac arrest was an independent determinant of inotrope score and was present in a relatively large proportion – particularly in the third inotrope score tertile – of donors compared to the donor population in the study by Dronavalli et al In addition, preoperative serum urea and C-reactive protein were determinants of inotrope score. These biomarkers are associated with illness severity, implying that patients who required higher amounts of inotropes after HTx were in poorer clinical condition preoperatively.

4.3 | Association of inotrope score with outcomes

In line with previous studies, we found that inotrope score was associated with long-term mortality up to five years, adjusted for age and gender, as well as morbidity. It is likely that inotrope score is a marker of increased disease severity and is therefore correlated with poor outcome. This is in agreement with the findings that after adjusting for female-to-male transplant and ischemia time, the association with mortality was attenuated. It can be hypothesized that female-to-male transplant and increased ischemia time, being known risk factors for primary graft dysfunction, might increase the amount of inotropic support required.

Exposure to high quantities of inotropes in itself may also be an additional contributor to increased morbidity and mortality via a number of mechanisms.[23] The most important side effects of inotropic medication are arrhythmia and increased myocardial oxygen consumption, which may further decrease cardiac function and may cause myocardial damage.[24] We did not record the occurrence of arrhythmia, as it is very challenging to attribute this specifically to the use of inotropic agents. However, arrhythmia may have contributed to the development of primary graft dysfunction and subsequently, increased inotrope dependency. In addition, high doses of catecholamines may cause metabolic disturbances, including impaired glucose metabolism, and may compromise immunity, increasing susceptibility to infections.[25] This may partly explain why patients exposed to inotropes have a higher risk of mortality. Indeed, there is still limited evidence for the beneficial effect of inotrope therapy in heart failure and low cardiac output syndrome on clinical outcomes.[26-28]

During the first 48 h after HTx, cardiac index and pulmonary artery pressures were similar between inotrope score tertiles, but there was a clear negative correlation between arterial blood pressure and inotrope score. Based on these data, we cannot conclude whether high doses of inotropes were given due to low blood pressure, for example in case of systemic vasoplegia, or whether both inotrope score and blood pressure were affected by a common determinant, such as low cardiac output. Nonetheless, this negative correlation between inotrope score and blood pressure shows that inotrope score reflects the patient's hemodynamic status.

We found that higher inotrope score was associated with initiation of CVVH. Acute kidney injury is associated with substantially increased risk of mortality following HTx.[29] The interaction between inotrope score and kidney function may be explained by a physiological mechanism, since impaired graft function and long cardiopulmonary bypass time combined with high doses of vasopressors may aggravate renal hypoperfusion. This may result in deteriorating kidney function and the requirement of replacement therapy. It should be considered that renal replacement therapy in itself can also cause hemodynamic instability and increased need for inotropic support due to multiple factors, including excessive ultrafiltration.[30] However, in 78% of patients requiring CVVH in our study, CVVH was initiated more than 48 h after HTx. Therefore, hemodynamic instability reflected by high inotrope score is likely to have contributed to impaired renal perfusion and requirement of CVVH.

In our study, inotrope score did not show an association with a cardiac index or other hemodynamic markers one year after transplantation. We hypothesize that poor initial graft function requiring large amounts of inotropic support does not affect long-term cardiac allograft function. This suggests that a high inotropic score is a measure of illness severity directly after transplantation, mimicking the early often critical phase directly after HTx, and is not necessarily by itself a marker of poor long-term cardiac outcomes.

4.4 | Limitations

This study has a number of limitations to consider. These limitations are primarily related to the historical cohort study design. Most importantly, data collection was dependent on accurate documentation in medical records. In addition, the relatively small sample size may have affected statistical power. Finally, comparing our results to existing literature was limited, as most research on inotrope score has focused on pediatric patients and studies used different modified calculations of inotrope score.

5 | CONCLUSION

Specific variables that are associated with primary graft dysfunction in HTx recipients are associated with higher inotrope scores after transplantation. Inotrope score by itself is associated with worse clinical outcome, initiation of CVVH, and ICU length of stay.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.